(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 114 734**
**B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **13.05.87**

(51) Int. Cl.[4]: **C 07 D 213/38,** A 61 K 31/44

(21) Application number: **84300210.6**

(22) Date of filing: **13.01.84**

(54) **Pyridinylmethylamino-arylic acids.**

(30) Priority: **19.01.83 US 459074**

(43) Date of publication of application:
**01.08.84 Bulletin 84/31**

(45) Publication of the grant of the patent:
**13.05.87 Bulletin 87/20**

(84) Designated Contracting States:
**BE CH DE FR GB IT LI NL SE**

(56) References cited:
**GB-A-1 253 743**
**US-A-3 226 394**
**US-A-3 654 290**
**US-A-3 862 953**

**Chemical Abstracts, no. 67, 1967, abstract 21789n**

(73) Proprietor: **THE UPJOHN COMPANY**
**301 Henrietta Street**
**Kalamazoo, Michigan 49001 (US)**

(72) Inventor: **Lin, Chiu-Hong,**
**c/o The Upjohn Company**
**301 Henrietta Street**
**Kalamazoo, MI 49001 (US)**

(74) Representative: **Perry, Robert Edward et al**
**GILL JENNINGS & EVERY 53-64 Chancery Lane**
**London WC2A 1HN (GB)**

**EP 0 114 734 B1**



Courier Press, Leamington Spa, England.

**Description**

The present invention relates to 2-, 3- and 4-pyridinylmethylamino-acrylic acids.

Since the discovery that human platelets convert the prostaglandin endoperoxide ($PGH_2$) into a labile pro-aggregatory molecule known as thromboxane $A_2$ ($TXA_2$), compounds have been sought, which selectively inhibit the biological activity of $TXA_2$. Such compounds may act in two different ways; by inhibiting the $TXA_2$ synthetase, or by being a receptor level antagonist of $TXA_2$. As therapeutic agents, $TXA_2$, synthetase inhibitors (especially selective inhibitors) are more useful. See, e.g. Gorman, Advances in Prostaglandin and Thromboxane Research, *6* (1980) 417, and references cited therein.

In mammalian metabolism, arachidonic acid is transformed to 12-L-hydroperoxy-5,8,10,14-eicosatetraenoic acid which is transformed to 12-L-lipoxygenase. See Hamberg *et al.*, Proc. Nat. Acad. Scie. *71* (1974) 3400—3404. Similarly, 5-lipoxygenase transforms arachidonic acid into 5-S-hydroxyperoxy-6,8,11,14-eicosatetraenoic acid. Thus, an agent which inhibits the action of lipoxygenase would be useful in treating or preventing untowards conditions associated with lipoxygenase products.

A number of $TXA_2$ synthetase inhibitors are known. For example, bi-heterocyclic 9,11-trideoxy-PGF-type compounds are disclosed in US—A—4112224; SQ 80,388 [1-(3-phenyl-2-propenyl)-1H-imidazole] is disclosed by Harris *et al.*, Advances in Prostaglandin and Thromboxane Research *6* (1980) 437; pyridine and its derivatives are disclosed by Miyamoto *et al.*, Advances in Prostaglandin and Thromboxane Research *6* (1980) 443; and in GB—A—2039903. See also Tai *et al.*, Advances in Prostaglandin and Thromboxane Research *6* (1980) 447. Other compounds which have been disclosed as thromboxane synthetase inhibitors include sodium p-benzyl-4-(1-oxo-2-(4-chlorobenzyl)-3-phenylpropyl)phenyl phosphate, imidazoles, nordihydroguaiaretic acid and 12-L-hydroperoxy-5,8,10,14-eicosatetraenoic acid (HETE). As noted in GB—A—2039903, however, the inhibitory activity of these latter compounds on thromboxane synthetase is very weak, making them unsatisfactory as practically effective medicines.

FR—B—1585085 discloses certain N-pyridinyl/anthranilic acids which are stated to be useful as analgesic, antipyretic, anti-inflammatory and anti-rheumatic agents. JP—A—75 111076 discloses certain pyridyloxy-phenylalkanoic or pyridyloxy-benzoic acid derivatives which are stated to be useful as anti-inflammatory, anti-rheumatic and analgesic agents. EP—A—0000176 discloses certain pyridyloxy-phenoxy-alkanoic acid derivatives which are stated to be useful as herbicides and plant growth regulators. Denny *et al.*, J. Med. Chem. *20* (1977) 1242 disclose pyridinyl-anthranilic acids.

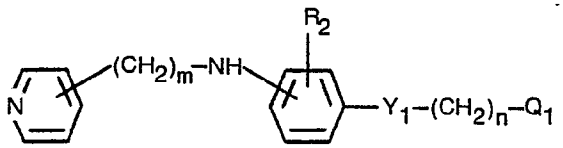
Certain 2-pyridinyl-phenylene compounds are disclosed in Derwent Farmdoc Nos. 20536F, 29402F, 11056T, 06401A, 11911B, 12380B and 50291C, and in C.A. 86:17135U. Other pyridinyl-phenylene compounds are disclosed in Derwent Farmdoc Nos. 75975R, 75002U and 03847D.

Certain 3-pyridinyl-δ-carboxylic acids having aza and phenylene groups in the side-chain are disclosed in EP—A—0100158, published 8.02.84. US—A—3654290 discloses certain N-amino-N-arylaminoalkylpyridines as intermediates for the preparation of certain 5-(pyridylalkyl)pyridoindole derivatives having anti-allergic activity.

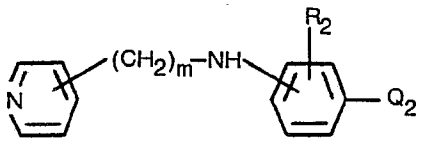
Chem. Abs. *67* (1967) 21789n discloses, inter alia, compounds of formula II (see below), wherein m is 1, $R_2$ is H and $Q_2$ is COOH. It is stated that "most of the compounds synthesised inhibited xanthine oxidase".

GB—A—1253743 discloses 4-pyridyl compounds of formula II, wherein m is 2 and, inter alia, $R_2$ and $Q_2$ are each H, halogen, alkyl, COOalkyl, alkoxy or $CF_3$; in Example 9 (i), $R_2$ is H and $Q_2$ is 4-$COOC_2H_5$. The utility of these compounds is said to be as chemical intermediates.

Novel compounds according to the present invention are of the formulae



I



II

wherein

m is an integer of from one to 6;

n is an integer of from one to 6;

$Y_1$ is —O—, —S—, —$NR_3$— or a valence bond;

$R_2$ is H, OH, $OCH_3$, $OOCCH_3$, F, Cl, Br, $CH_3$, $CF_3$, $N(CH_3)_2$, $NO_2$, SH or $SCH_3$;

$Q_1$ is $COOR_1$, $CH_2OH$, $CH_2SH$, $NHR_3$ or 1-tetrazolyl;

in which $R_1$ is selected from hydrogen, a pharmacologically acceptable cation, $C_{1-12}$ alkyl, $C_{3-10}$ cycloalkyl, $C_{7-12}$ aralkyl, phenyl, phenyl substituted up to 3 times by chlorine atoms of $C_{1-3}$ alkyl groups, or phenyl para-substituted by acetamido, benzamido, acetamidobenzamido, benzamidobenzamido, ureido,

acetoxy, benzyloxy, aminocarbonyloxy, methoxycarbonyloxy, benzoyl, acetamidobenzoyl, acetamidobenzoyloxy or ureidoiminomethyl; and $R_3$ is hydrogen, $C_{1-5}$ alkyl or CHO; and $Q_2$ is $COOR_1$ or 1-tetrazolyl, provided that $R_2$ is OH when $Q_2$ is $COOR_1$ and $R_1$ is hydrogen, alkyl or a pharmocologically acceptable cation.

Compounds of the present invention may be prepared by the synthetic routes shown in Charts A, B and C. The respective starting materials (A—1, B—1, C—1) are either available or can be synthesised by known processes; see Hendrickson, J.A.C.S. *93* (1971) 6854.

Chart A relates to the preparation of compounds of formula I ($Y_1$ is a valence bond, $R_2$ is OH, $Q_1$ is $COOR_1$) or formula II ($R_2$ is OH, $Q_2$ is $COOR_1$), but the same synthesis can be used for all definitions of $R_2$, i.e. when $R_2$ is not OH.

An aminosalicylic acid (A—1) is treated with diazomethane in methanol. The resultant ester (A—2) is reacted with an aldehyde (A—2A) to yield the corresponding imine which is reduced with sodium borohydride. The resultant compound (A—3) is converted to a pharmacologically-acceptable salt by means well-known in the art, e.g. treatment with sodium hydroxide in methanol, to yield the formula A—4 compound.

Chart B relates to the preparation of compounds of formula I ($Y_1$ is O or S, $Q_1$ is $COOR_1$).

A hydroxyaniline or aminothiophenol derivative (B—1) is converted to a diacetate (B—2) by means well-known in the art, e.g. acetic anhydride in pyridine. The diacetate is selectively hydrolysed utilising potassium carbonate in methanol. The resultant acetamidophenol or acetamidothiophenol derivative (B—3) is alkylated, utilising sodium hydride or potassium carbonate as a base and dimethylformamide, glyme, tetrahydrofuran or acetone as a solvent. The product (B—4) is treated with strong acid such as hydrochloric acid in aqueous alcoholic solvent (see, e.g. Organic Synthesis, Coll. Vol. I, III) with or without heating. The resultant aniline derivative (B—5) is heated with an aldehyde (B—5A) to yield an imine which is reduced with sodium borohydride, to give the formula B—6 product. The corresponding pharmacologically-acceptable salts may be prepared as described above.

Chart C relates to the preparation of compounds of formula I ($Y_1$ is NH, $Q_1$ is $COOR_1$).

A nitroaniline derivative (C—1) is thermally condensed with an aldehyde (C—1A) to yield an imine which is reduced with sodium borohydride. The resultant compound (C—2) is acetylated with acetic anhydride in pyridine. The nitro group of the resultant acetamide derivative (C—3) is reduced by methods known in the art (see, e.g. Compendium of Organic Synthetic Methods, Vol. 2, p. 104; Vol. 4, p. 162). The resultant aniline derivative (C—4) is condensed with a methyl ω-formylalkanoate (C—4A), e.g. the methyl ester of glyoxalic acid, to yield an amine which is reduced with sodium borohydride. The resultant compound (C—5) is subjected to acidic hydrolysis, as described above, to remove the acetyl group. Alternatively, the aniline derivative (C—4) is acetylated to give the diacetate (C—8) which is alkylated as described in Chart B, and the alkylated compound (C—9) is subjected to acidic hydrolysis, to afford the formula C—6 product. Pharmacologically-acceptable salts may be prepared, as described above, to yield the formula C—7 compound.

Preferred compounds of the invention are those of formula I in which m is one, $Y_1$ is O and $Q_1$ is $COOR_1$, and those of formula II in which m is one and, preferably, $Q_1$ is $COOR_1$. In these cases, it is particularly preferred that $R_1$ is hydrogen, methyl, sodium potassium or calcium, and $R_2$ is hydrogen, hydroxy, methyl, acetoxy, fluoro or trifluoromethyl. The compounds of Examples 2 and 3 are the most preferred compounds of the invention.

In this specification "$C_{1-12}$ alkyl" means methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, docecyl, and isomeric forms thereof.

Examples of $C_{3-10}$ cycloalkyl, which includes alkyl-substituted cycloalkyl, are cyclopropyl, 2-methylcyclopropyl, 2,2-dimethylcyclopropyl, 2,3-diethylcyclopropyl, 2-butylcyclopropyl, cyclobutyl, 2-methylcyclobutyl, 3-propylcyclobutyl, 2,3,4-triethylcyclobutyl, cyclopentyl, 2,2-dimethylcyclopentyl, 2-pentylcyclopentyl, 3-tert-butylcyclopentyl, cyclohexyl, 4-tert-butylcyclohexyl, 3-isopropylcyclohexyl, 2,2-dimethylcyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl.

Examples of $C_{7-12}$ aralkyl are benzyl, 2-phenylethyl, 1-phenylethyl, 2-phenylpropyl, 4-phenylbutyl, 3-phenylbutyl, 2-(1-naphthylethyl) and 1-(2-naphthylmethyl).

Examples of phenyl substituted up to 3 times by chlorine atoms or $C_{1-3}$ alkyl groups are p-chlorophenyl, m-chlorophenyl, 2,4-dichlorophenyl, 2,4,6-trichlorophenyl, p-tolyl, m-tolyl, o-tolyl, p-ethylphenyl, 2,5-dimethylphenyl, 4-chloro-2-methylphenyl, and 2,4-dichloro-3-methylphenyl.

The compounds of the present invention may be in the form of pharmacologically acceptable salts. These salts are formed when $R_1$ is a pharmacologically acceptable cation. Such cations include: pharmacologically acceptable metal cations, ammonium, amine cations, or quaternary ammonium cations.

Especially preferred metal cations are those derived from the alkali metals, e.g., lithium, sodium, and potassium, and from the alkaline earth metals, e.g., magnesium and calcium, although cationic forms of other metals, e.g., aluminum, zinc, and iron are within the scope of this invention.

Pharmacologically acceptable amine cations are those derived from primary, secondary, or tertiary amines. Examples of suitable amines are methylamine, dimethylamine, trimethylamine, ethylamine, dibutylamine, triisopropylamine, N-methylhexylamine, decylamine, dodecylamine, allylamine, crotylamine, cyclopentylamine, dicyclohexylamine, benzylamine, dibenzylamine, α-phenylethylamine, β-phenylethylamine, ethylenediamine, diethylenetriamine, and the like aliphatic, cycloaliphatic, araliphatic

amines containing up to and including about 18 carbon atoms, as well as heterocyclic amines, e.g., piperidine, morpholine, pyrrolidine, piperazine, and lower-alkyl derivatives thereof, e.g.,

1-methylpiperidine,
4-ethylmorpholine,
1-isopropylpyrrolidine,
2-methylpyrrolidine,
1,4-dimethylpiperazine,
2-methylpiperidine,

and the like, as well as amines containing water-solubilizing or hydrophilic groups, e.g.,

mono-, di-, and triethanolamine,
ethyldiethanolamine,
N-butylethanolamine,
2-amino-1-butanol,
2-amino-2-ethyl-1,3-propanediol,
2-amino-2-methyl-1-propanol,
tris(hydroxymethyl)aminomethane,
N-phenylethanolamine,
N-(p-tert-amylpenyl)diethanolamine,
glactamine,
N-methylglycamine,
N-methylglucosamine,
ephedrine,
Phenylephrine,
epinephrine,
procaine,

and the like. Further useful amine salts are the basic amino acid salts, e.g.,

lysine and
arginine.

Examples of suitable pharmacologically acceptable quaternary ammonium cations are

tetramethylammonium,
tetraethylammonium,
benzyltrimethylammonium,
phenyltriethylammonium, and the like.

Pharmaceutically acceptable acid addition salts are formed at the heterocyclic amine moiety and are also useful for administering the compounds of this invention. These salts include hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, maleate, malate, succinate, tartrate, and the like. They are prepared by methods well known in the art.

The compounds of the present invention will be named herein using the Chemical Abstracts numbering system (see Naming and Indexing of Chemical Substances for Chemical Abstracts during the Ninth Collective Period (1972—1976), a reprint of section IV from the Volume 76 Index Guide).

The compounds of the present invention were tested for $TXA_2$ inhibition as follows:

Rabbit aortic strips were superfused in series with Krebs solution. Thromboxane $A_2$ ($TXA_2$) was generated by mixing prostaglandin $H_2$ ($PGH_2$) with human platelet microsomes (HPM).

Potential inhibitors were tested by comparing the response of the rabbit aorta to the amount of $TXA_2$ produced by mixing $PGH_2$ and HPM without the test compound in the reaction medium and then the amount of $TXA_2$ produced when the test compound was added to the HPM 5 minutes before the HPM was mixed with $PGH_2$. By this means compounds which selectively inhibit $TXA_2$ synthetase are found. For a discussion of $TXA_2$ synthetase inhibition testing see, e.g., R. Gorman, *supra.*

Using this test system, 4-(3-pyridinylmethylamino)salicylic acid, sodium salt (Example 2) has been shown to be the most effective in inhibiting $TXA_2$ formation. This compound has an approximate $ED_{50}$ in this system of between 10 and 100 ng/ml.

The compounds of the present invention were also tested for 5-lipoxygenase inhibition. Arachidonic acid is added to washed human platlets and the oxygen uptake is measured using oxygraph cells. A decrease of oxygen uptake versus the control cell indicates inhibition of lipoxygenase. For a fuller description of the procedure see, Wallach, et al., Biochim. Biophys. Acta. 231:445 (1976).

Using this system, 5-(3-pyridinylmethylamino)salicylic acid, methyl ester (Example 3), has been shown to be the most effective, having an approximate $ED_{50}$ in this system of $1 \times 10^{-5}$ Molar.

Thus, some of the novel compounds of this invention have been shown to be active as inhibitors of the thromboxane synthetase enzyme system and some of the compounds of this invention have been shown to be active as inhibitors of the lipoxygenase enzyme system. Some of these compounds are effective in both systems. All of the compounds of this invention are active as inhibitors of at least one of these two systems. Accordingly, these novel compounds are useful for administration to mammals, including humans, whenever it is desirable medically to inhibit either of these enzyme systems.

Thromboxane synthetase inhibitors are useful to treat inflammation, to inhibit platlet aggregation, and

to treat or prevent gastrointestinal ulcer formation. For a discussion of the utility of $TXA_2$ inhibitors, see, e.g. Derwent Farmdoc Nos. 18399B; 72896B; 72897B; 63409B; 03755C; 03768C; and 50111C.

Thromboxane synthetase converts $PGH_2$ (prostaglandin endoperoxide) into $TXA_2$. $PGH_2$ is also converted to prostacyclin, $PGD_2$, and other compounds by other enzymes. Thus, because the compounds of this invention inhibit thromboxane $A_2$ synthetase, they increase the $PGH_2$ substrate and thus increase the amount of endogenous prostacyclin. Therefore, they are also useful for many of the pharmacological purposes for which prostacyclin is employed.

Prostacyclin and a thromboxane synthetase inhibitor have both been shown to be effective in controlling tumor cell metastasis, see, e.g., K. Honn, et al., "Thromboxane Synthetase Inhibitors and Prostacyclin Can Control Tumor Cell Metastasis," an Abstract of the Twentieth Annual Meeting of the American Society for Cell Biology, in the Journal of Cell Biology, 87:64 (1980).

Similarly, prostacyclin has been shown to be an effective antihypertensive agent. The compounds of the present invention are also used for this purpose; see, for example, GB—A—2039903.

For a general discussion of the utility of $TXA_2$ synthetase inhibitors which increase endogenous prostacyclin, see, Aiken, et al. J. Pharmacol. Exp. Ther., 219:299 (1981).

Lipoxygenase inhibitors are also useful as to treat inflammation and to inhibit platlet aggregation. Thus, Hammerström, et al. Science 197:994—996 (1977) notes the role of 12-lipoxygenase in psoriasis. Doig, et al., Prostaglandins 20:1007—1019 (1980) and Lin, et al., J. Clin. Invest. 70:1058 (1982) disclose that 5-lipoxygenase inhibitors block platlet thrombus formation. Dawson, et al., in SRS—A and Leukotrines, 219—226 (Wiley and Sons 1981) note that 5-lipoxygenase inhibitors block neutrophil "recruitment" during inflammatory diseases such as arthritis.

In addition, 5-lipoygenase inhibitors may prevent the production of slow-reacting substance of anaphylaxis (SRS—A), now known to be a mixture of leukotrienes. (All luekotrienes are synthesized using 5-lipoxygenase.) SRS—A mediates the symptoms and pathophysiology of asthma. See Murphy, et al., Proc. Nat. Acad. Sci. USA 76, 4275—4279 (1979). Thus, the 5-lipoxygenase inhibitors disclosed herein may be useful in the treatment of asthma.

5-lipoxygenase products have been implicated in essential hypertension (Chand, et al., Microcirculation 1:111—123 (1981), and gout (Rae, et al., Lancet 1122—1124 (Nov. 20, 1982) indicating that the 5-lipoxygenase inhibitors disclosed herein are useful in treating these conditions as well. Further, neutrophil depletion, such as that induced by 5-lipoxygenase inhibitors, has been shown to cause a significant decrease in infarct size following circumflex artery occlusion. See Romson, et al., Circulation 66:85 (1982). Thus, the 5-lipoxygenase inhibitors herein may be useful in the protection of the myocardium following infarct.

All of the compounds of the present invention are $TXA_2$ synthetase inhibitors or 5-lipoxygenase inhibitors, and some have both properties. Thus, all of the compounds of this invention are useful as anti-inflammatory agents and as platlet aggregation inhibitors. These are preferred uses for these compounds.

Thus, for example, all of these novel compounds are useful as antiinflammatory agents in mammals and especially humans, and for this purpose, are administered systemically and preferably orally. For oral administration, a dose range of 0.05 to 50 mg per kg of human body weight is used to give relief from pain associated with inflammatory disorders such as rheumatoid arthritis. They are also administered intravenously in aggravated cases of inflammation, preferably in a dose range of 0.01 to 100 µg per kg per minute until relief from pain is attained. When used for these purposes, these novel compounds cause fewer and lesser undesirable side effects than do the known synthetase inhibitors used to treat inflammation, for example, aspirin and indomethacin. When these novel compounds are administered orally, they are formulated as tablets, capsules, or as liquid preparations, with the usual pharmaceutical carriers, binders, and the like. For intravenous use, sterile isotonic solutions are preferred.

These compounds are useful whenever it is desired to inhibit platelet aggregation, to reduce the adhesive character of platelets, and remove or prevent the formation of thrombi in mammals, including man, rabbits, dogs, and rats. For example, these compounds are useful in the treatment and prevention of myocardial infarcts, to treat and prevent post-operative thrombosis, to promote patency of vascular grafts following surgery, and to treat conditions such as atherosclerosis, arteriosclerosis, blood clotting defects due to lipemia, and other clinical conditions in which the underlying etiology is associated with lipid imbalance or hyperlipidemia. For these purposes, these compounds are administered systemically, e.g., intravenously, subcutaneously, intramuscularly, and in the form of sterile implants for prolonged action. For rapid response especially in emergency situations, the intravenous route of administration is preferred. Doses in the range about 0.005 to about 20 mg per kg of body weight per day are used, the exact dose depending on the age, weight, and condition of the patient or animal, and on the frequency and route of administration.

These compounds are further useful as additives to blood, blood products, blood substitutes, or other fluids which are used in artificial extracorporeal circulation or perfusion of isolated body portions, e.g., limbs and organs, whether attached to the original body, detached and being preserved or prepared for transplant, or attached to a new body. During these circulations and perfusions, aggregated platelets tend to block the blood vessels and portions of the circulation apparatus. This blocking is avoided by the presence of these compounds. For this purpose, the compound is added gradually or in single or multiple portions to the circulating blood, to the blood of the donor animal, to the perfused body portion, attached

or detached, to the recipient, or to two or all of these at a total steady state dose of about 0.001 to 10 mg per liter of circulating fluid. It is especially useful to use these compounds in laboratory animals, e.g., cats, dogs, rabbits, monkeys, and rats, for these purposes in order to develop new methods and techniques for organ and limb transplants.

The novel compounds are used for the purposes described above in the free acid form, in ester form, and in the pharmacologically acceptable salt form. When the ester form is used, the ester is any of those within the above definition of $R_1$. However, it is preferred that the ester be alkyl of one to 12 carbon atoms, inclusive. Of the alkyl esters, methyl and ethyl are especially preferred for optimum absorption of the compound by the body of experimental animal system; and straight-chain octyl, nonyl, decyl, undecyl, and dodecyl are especially preferred for prolonged activity in the body or experimental animal.

Thus, the compounds are administered orally in forms such as pills, capsules, solutions or suspensions. They may also be administered rectally or vaginally in forms such as suppositories or bougies. They may also be introduced intravenously, subcutaneously, or intramuscularly using sterile injectable forms known to the pharmaceutical art.

In general the preferred form of administration is orally.

The following Preparations illustrate synthetic steps towards, and the Examples illustrate the preparation of, compounds of the present invention. The compounds of formula I are defined by representing the pyridyl group as $Z_1$ and positions on the benzene ring with respect to $Y_1$. "Celite" is a registered Trade Mark.

Preparation 1

4-Aminosalicylic Acid, Methyl Ester

Refer to Chart A, (conversion of A—1 to A—2).

A round-bottomed flask equipped with a magnetic stirring bar is charged with 15.3 g (0.1 mol) of 4-aminosalicylic acid and 100 ml of methanol. Freshly prepared diazomethane in ether is added until thin layer chromatography (TCL) indicates no starting material is remaining. The solvent is removed in vacuo and the residue is dissolved in hot ethyl acetate-hexane, decolorized with activated charcoal, filtered through a pad of Celite, and concentrated in vacuo. The residue is recrystallized from the ethyl acetate-hexane. The first crop affords 12.43 g of the second crop 1.10 g for a total of 13.53 g (81%) of crystals having a melting point (mp) of 119°—12;°C NMR ($CDCl_3$, TMS, δ) peaks are observed at 7.70—6.00, 4.10, and 3.86. TLC (silica gel GF), reveals an Rf of 0.39 in hexane-acetone (2:1).

Preparation 2

5-Aminosalicylic Acid, Methyl Ester

Refer to Chart A (conversion of A—1 to A—2).

A round-bottomed flask equipped with a magnetic stirring bar is charged with 30.6 (0.2 mol) of 5-aminosalicylic acid (Aldrich) and 200 ml of methanol. Freshly prepared diazomethane in ether is added until TLC indicates no starting material remains. After the removal of solvent in vacuo a black solid is obtained. This solid is subjected to column chromatography using 1.2 kg of silica gel (EM, 63—200 μ), eluting with methylene chloride-ethyl acetate (10:1), and collecting 300 ml fractions. Fractions (19—22) are homogeneous by TLC and are combined and concentrated in vacuo to give a brown oil (2.63 g). This material is less polar than the desired product and NMR reveals an extra peak at δ 2.80 as a singlet. Fractions (24—60) are homogeneous by TLC and are combined and concentrated in vacuo to give a yellow solid (31.8 g). Recrystallization from hexane-ethyl acetate affords 25.3 g (75.8%) of yellow crystals with a melting point of 95°—96°C; NMR ($CDCl_3$, TMS, δ) peaks are observed at 7.38—6.80 (-aryl-), 3.92, 10.28 and 3.50. TLC (silica gel GF), reveals an Rf of 0.45 in hexane-acetone (1:1).

Example 1

4-(3-Pyridinylmethylamino)salicylic Acid, Methyl Ester (Formula I: $Z_1$ is 3-pyridyl; m is 1, $Z_1$-$(CH_2)_m$-NH is para, $R_2$ is ortho hydroxy, $Y_1$ is a valence bond, n is zero, and $Q_1$ is $—CH_2CH_3$)

A round-bottomed flask equipped with a magnetic stirring bar, a Dean-Stark receiver, and a reflux condenser is charged with 3.34 g (20.0 mmol) of 4-aminosalicylic acid, methyl ester (Preparation 1) 2.14 g (20.0 mmol) of 3-pyridinecarboxaldehyde (Aldrich), 0.19 g (1.0 mmol) of p-toluenesulfonic acid, and 300 ml of benzene under a nitrogen atmosphere. The mixture is heated to reflux (bath temperature 110°C) for 24 hours. The solvent is removed in vacuo and the residue is dissolved in 200 ml of methanol. The solution is cooled to 0—5°C and sodium borohydride powder (2.78 g, 60.0 mmol) is added over a period of 5 minutes. After stirring the mixture for one hour, the reaction is quenched with aqueous saturated ammonium chloride and the methanol is removed in vacuo. The residue is treated with brine and extracted with ethyl acetate (1L). The organic layer is washed with brine and dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo afford a pale yellow solid. TLC analysis shows that the imine is not completely reduced. Therefore the solid is redissolved in 200 ml of methanol and reacted this time with 7.6 g (200.0 mmol) of sodium borohydride at 0—5°C. After one hour, the mixture is worked up as above to give the crude product (4.6 g). Liquid chromatography is carried out by using 388 g of silica gel (EM, 40—63μ), eluting with methylene chloride-acetone (4:1), and collecting 40 ml fractions. Fractions (15—22) are homogeneous by TLC and are combined and concentrated in vacuo to give 1.02 g (30%) of recovered

starting material, 4-aminosalicylic acid, methyl ester. Fractions (44—63) are homogeneous by TLC and are combined and concentrated in vacuo to give 2.40 g of the titled product. Recrystallization from hexane-ethyl acetate affords a white solid (a first crop of 1.89 g and a second crop of 0.26 g for a total of 2.14 g a 41% yield) with a melting point of 94—95°C.

The NMR ($CD_3OD$ + $D_2O$, TMS, δ) reveals peaks at 8.70—6.08, 4.38, and 3.88.

The IR (Nujol, vmax) reveals peaks at 3235, 3152, 3047, 3006, 2956, 1666, 1626, 1578, 1542, 1440, 1337, 1272, 1264, 1199, 1188, 1096, and 1031 $cm^{-1}$.

Mass Spectrum yields ions at m/e 258.0995, 226, 211, 197, 180, 169, 148, 136, 106, and 92.

C:H:N Analysis yields: Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85; Found: C, 64.73; H, 5.46; N, 10.71.

TLC Analysis (Silica Gel GF) yields an Rf of 0.34 in methylene chloride-acetone (2:1).

Example 2

4-(3-Pyridinylmethylamino)salicylic Acid, Sodium Salt (The sodium salt of Example 1)

A round-bottomed flask equipped with a magnetic stirring bar is charged with 516.6 mg (2.0 mmol) of the compound of Example 1, 2.0 ml (2.0 mmol) of 1N aqueous sodium hydroxide, and 4.0 ml of methanol. The resulting yellow solution is stirred at room temperature for 24 hours. TLC analysis shows no reaction occurs. Therefore 2.0 ml (2.0 mmol) of 1N aqueous sodium hydroxide and 2.0 ml of methanol are added and the solution is stirred for an additional 24 hours. TLC analysis shows only about 50% completion. Another portion of 2.0 ml (2.0 mmol) of 1N aqueous sodium hydroxide and 2.0 ml of methanol is added. The mixture is heated at 50°C and stirred for 48 hr. TLC analysis shows no starting material remaining. Methanol-water is removed in vacuo and the residue is dissolved in about 10 ml of water and then the solution is diluted with 600 ml of acetone and the cloudy solution is allowed to stand in the refrigerator for 2 days. The solution is filtered and concentrated in vacuo. The residue is treated with toluene-acetone and the resulting light red solid is separated. The red solid is dried in vacuo to obtain 503.0 mg of the titled sodium salt.

NMR ($CDCl_3$, TMS, δ) reveals peaks at 8.72—6.00 and 4.43.

IR (Nujol, vmax) reveals peaks at 3357, 2954, 1635, 1589, 1583, 1562, 1484, 1439, 1433, 1386, 1356, 1333, 1329, 1201, 1192, 1167, 835 and 769 $cm^{-1}$.

TLC Analysis (Silica Gel GF) yields an Rf of 0.03 in methylene chloride-acetone (2:1).

Example 3

5-(3-Pyridinylmethylamino)salicylic Acid, Methyl Ester (Formula I: $Z_1$ is 3-pyridyl, m is 1, $Z_1$-$(CH_2)_m$—NH— is meta, $R_2$ is ortho hydroxy, $Y_1$ is a valence bond, n is zero, and $Q_1$ is —$CO_2CH_3$)

Refer to Chart A (conversion of A—2 to A—3).

A round-bottomed flask equipped with a magnetic stirring bar, a Dean-Stark moisture receiver, and a reflux condenser is charged with 3.34 g (20.0 mmol) of 5-aminosalicylic acid, methyl ester (Preparation 2), 2.14 g (20.0 mmol) of 3-pyridinecarboxaldehyde (Aldrich), 0.19 g (1.0 mmol) of p-toluenesulfonic acid, and 120 ml of benzene-glyme (5:1) under a nitrogen atmosphere. The mixture is heated to reflux (bath temperature, 110°C) for 2 hours. TLC shows no starting material remaining. The solvent is removed in vacuo to give a brown oil. This oil is dissolved in 120 ml of methanol and the solution is cooled to 0—5°C with an ice-water bath. Sodium borohydride powder (2.28 g, 60.0 mmol) is added over a period of 5 minutes under a nitrogen atmosphere. The resulting light brown solution is stirred for one hour. TLC shows no starting material remaining. The reaction is quenched with 50 ml of saturated aqueous ammonium chloride and the methanol is removed in vacuo. The residue is treated with 50 ml of 1N aqueous sodium hydroxide and extracted twice with 400 ml of ethyl acetate. The organic layer is washed with 20 ml of 1N aqueous sodium hydroxide, brine, and dried over anhydrous magnesium sulfate. Filtration and concentration afford a brown oil. Liquid chromatography is carried out by using 166 g of silica gel (EM, 40—63μ), eluting with methylene chloride-acetone (4:1), and collecting 30 ml fractions. Fractions (26—53) are homogeneous by TLC and are combined and concentrated in vacuo to give a yellow solid. Recrystallization from hexane-ethyl acetate affords a yellow solid (4.10 g, 79.3%) with a melting point of 79—80°C.

The NMR ($CDCl_3$, TMS, δ) reveals peaks at 8.75—6.84, 4.32, and 3.90.

The IR (Nujol, vmax) reveals peaks at 3310, 3245, 1685, 1620, 1530, 1450, 1290, 1235, 1180, 1075, 785 and 710 $cm^{-1}$.

The Mass Spectrum yields ions at m/e 258.0990, 226, 197, 181, 169, 148, 134, 120, 106, and 92.

C:H:N Analysis yields: Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 64,84; H, 5.49; N, 10.69.

TLC Analysis (Silica Gel GF) yields an Rf of 0.33 in methylene chloride-acetone (2:1).

Example 4

5-(3-Pyridinylmethylamino)salicylic Acid, Sodium Salt (The sodium salt of Example 3)

A round-bottomed flask equipped with a magnetic stirring bar is charged with 1.3 g (5.0 mmol) of the compound of Example 3, 5.1 ml (5.1 mmol) of 1N aqueous sodium hydroxide, and 5.1 ml of methanol under a nitrogen atmosphere. The mixture is stirred at room temperature for 5 days. The solution turns deep

brown in color. The mixture is lyophilized and the solid is washed with acetone to give 520 mg of a dark brown solid.

The NMR ($CDCl_3$ + $D_2O$, TMS, δ) yields peaks at 8.75—6.84 and 4.42.

TLC Analysis (Silica Gel GF) yields an Rf of 0.02 in methylene chloride-acetone (2:1).

Example 5

5-(2-Pyridinylmethylamino)salicylic Acid, Methyl Ester (Formula I: $Z_1$ is 2-pyridyl, $Z_1$—$(CH_2)_m$—NH is meta, $R_2$ is ortho hydroxy, $Y_1$ is a valence bond, n is zero, and $Q_1$ is —$CO_2CH_3$)

Refer to Chart A (conversion of 1—2 to A—3).

A round-bottomed flask equipped with a magnetic stirring bar, a Dean-Stark moisture receiver, and a condenser, is charged with 3.34 g (20 mmol) of the compound of Preparation 2, 2.14 g (20 mmol) of 2-pyridinecarboxaldehyde, 0.19 g (1.0 mmol) of p-toluene sulfonic acid, and 120 ml of benzene-glyme (5:1). The resulting deep brown solution is heated for 3 hours. TLC analysis shows no starting material remaining. The solvent is removed in vacuo to give a brown oil. The oil is dissolved in 100 ml of methanol and the solution is cooled to $-20 \sim -10$°C under a nitrogen atmospher. Sodium borohydride powder (2.28 g, 60 mmol) is added over a period of 5 minutes. After stirring for 30 minutes, TLC analysis shows no starting material remaining. The reaction is quenched with 50 ml of saturated aqueous ammonium chloride and methanol is removed in vacuo. The residue is extracted with 500 ml of ethyl acetate. The organic layer is washed with 1N aqueous sodium hydroxide (50 ml), brine, and dried over anhydrous magnesium sulfate. Filtration and concentration afford a brown oil. Purification is carried out by liquid chromatography, using 388 g of silica gel (EM, 40—63μ), eluting with methylene chloride-acetone (10:1), and collecting 40 ml fractions. Fractions (58—60) are homogeneous by TLC and are combined and concentrated in vacuo to give 4.06 g of crude titled product. Recrystallization from hexane-ethyl acetate affords a yellow solid (3.87 g, 75%) with a melting point of 78—85°C.

The NMR ($CDCl_3$, TMS, δ) reveals peaks at 10.26, 4.58, 8.72—6.80, 4.40 and 3.96.

The Mass Spectrum yields ions at m/e 258.1010, 266, 198, 169, and 93.

C:H:N Analysis yields: Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 64.92; H, 5.52; N, 10.84.

TLC Analysis (Silica Gel GF) yields an Rf of 0.5 in methylene chloride-acetone (2:1).

Example 6

5-(2-Pyridinylmethylamino)salicylic Acid, Sodium Salt (the sodium salt of Example 5)

A round-bottomed flask equipped with a magnetic stirring bar is charged with 1.29 g (5.0 mmol) of the compound of Example 5, 5.1 ml (5.1 mmol) of 1N aqueous sodium hydroxide and 5.1 ml of methanol. The resulting deep red solution is stirred at room temperature under a nitrogen atmosphere for 48 hours. TLC shows no starting material remains. The mixture is lyophilized. The solid is stirred in hot acetone and then the acetone is removed by filtration. The titled sodium salt is isolated as a light red solid (510 mg).

The NMR Spectrum ($CD_3OD$ + $D_2O$, TMS, δ) reveals peaks at 8.83—6.63 and 4.46.

TLC Analysis (Silica Gel GF) yields an Rf of 0.01 in methylene chloride-acetone (2:1).

Example 7

5-(4-Pyridinylmethylamine)salicylic Acid, Methyl Ester (Formula I: $Z_1$ is 4-pyridyl, $Z_1$ is 4-pyridyl, $Z_1$—$(CH_2)_m$—NH is meta, $R_2$ is ortho hydroxy, $Y_1$ is a valence bond, n is zero, and $Q_1$ is $CO_2CH_3$)

Refer to Chart A (conversion of A—2 to A—3).

A round-bottomed flask equipped with a magnetic stirring bar, a Dean-Stark moisture receiver, and reflux condenser is charged with 3,34 g (20.0 mmol) of 5-aminosalicylic acid, methyl ester (Preparation 2), 2.14 g (20.0 mmol) of 4-pyridinecarboxaldehyde (Aldrich), 0.19 g (1.0 mmol) of p-toluene sulfonic acid, and 120 ml of benzene-glyme (5:1) under a nitrogen atmosphere. The mixture is heated to reflux (bath temperature, 110°C) for 2 hours. The solvent is removed in vacuo to give the imine. This imine is dissolved in 120 ml of methanol and the solution is cooled to 0—5°C with an ice-water bath. Sodium borohydride powder (2.28 g, 60.0 mmol) is added over a period of 5 minutes under a nitrogen atmosphere. The resulting solution is stirred for one hour. The reaction is quenched with 50 ml of saturated aqueous ammonium chloride and the methanol is removed in vacuo. The residue is treated with 50 ml of 1N aqueous sodium hydroxide and extracted twice with 400 ml of ethyl acetate. The organic layer is washed with 20 ml of 1N aqueous sodium hydroxide, brine, and dried over anhydrous magnesium sulfate. Filtration and concentration afford the crude product. Liquid chromatography followed by recrystallization afford the titled product.

Example 8

5-(4-Pyridinylmethylamino)salicylic Acid, Sodium Salt (The sodium salt of Example 7)

A round-bottomed flask equipped with a magnetic stirring bar is charged with 1.3 g (5.0 mmol) of the compound of Example 7, 5.1 ml (5.1 mmol) of 1N aqueous sodium hydroxide, and 5.1 ml of methanol under a nitrogen atmosphere. The mixture is stirred at room temperature until TLC analysis shows no starting material remaining. The mixture is lyophilized and recrystallized from acetone-water to give the titled product.

Preparation 3

4-Acetamido-2-methyl-phenylacetate

Refer to Chart B (conversion of B—1 to B—2 wherein $R_2$ is ortho-$CH_3$, $Y_1$ is —O—)

A round-bottomed flask equipped with a magnetic stirring bar is charged with 12.3 g (0.1 mol) of 4-amino-o-cresol (Aldrich), 40 ml of acetic anhydride, and 40 ml of pyridine. The resulting mixture is stirred at room temperature until TLC shows no starting material remaining. The solution is cooled to 0—5°C with an ice-water bath and treated with 10 ml of water. After stirring the mixture for 30 minutes, saturated aqueous sodium bicarbonate is added slowly until the pH of the mixture reads 7—8. Extraction with ethyl acetate is followed by washing the organic layer with water and brine. Drying over anhydrous magnesium sulfate, filtration, and concentration in vacuo afford the crude product. Purification is carried out by chromatography or crystallization to give the titled product.

Preparation 4

4-Acetamido-2-methyl-phenol

Refer to Chart B (conversion of B—2 to B—3 wherein $R_2$ is ortho-$CH_3$, $Y_1$ is —O—).

A round-bottomed flask equipped with a magnetic stirring bar is charged with 20.7 g (0.1 mol) of 4-acetamido-2-methyl-phenyl acetate (Preparation 3), 20.7 g (0.15 mol) of potassium carbonate, and 1L of methanol. The resulting mixture is stirred at room temperature under a nitrogen atmosphere for 24 hours. Methanol is removed in vacuo and the residue is neutralized with 10% aqueous sodium bisulfate to pH ~ 7. The mixture is extracted with ethyl acetate. The organic layer is washed with brine and dried over anhydrous magnesium sulfate. Filtration and concentration afford the crude product which is purified by either recystallization or chromatography to give the titled product.

Preparation 5

(4-Acetamido-2-methyl-phenoxy)Acetic Acid, Methyl Ester

Refer to Chart B (conversion of B—3 to B—4 wherein $R_2$ is ortho-$CH_3$, $Y_1$ is —O—).

A round-bottomed flask equipped with a magnetic stirring bar is charged with 16.4 g (0.1 mol) of 4-acetamido-2-methyl-phenol (Preparation 4), 16.5 g (0.12 mol) of potassium carbonate, 30.6 g (0.2 mol) of bromoacetate (Aldrich), and 200 ml of glyme. The mixture is stirred at room temperature for 24 hrs. Glyme is removed in vacuo and the residue is neutralized with cold 10% aqueous sodium bisulfate until the pH of the mixture is 7—8. The mixture is extracted with ethyl acetate. The organic layer is washed with brine and dried over anhydrous magnesium sulfate. Filtration and concentration afford the crude product which is purified by either recrystallization or chromatography to give the titled product.

Preparation 6

(4-Amino-2-methyl-phenoxy)acetic Acid, Methyl Ester

Refer to Chart B (conversion of B—4 to B—5 wherein $R_2$ is ortho-$CH_3$, $Y_1$ is —O—, n is 1)

A round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser is charged with 23.1 g (0.1 mol) of 4-Acetamido-2-methyl-phenoxy)-acetic acid, methyl ester (Preparation 5), 25 ml of 95% ethanol and 25 ml of concentrated hydrochloric acid (Organic Synthesis. Coll. Vol. I, III). The mixture is refluxed until TLC shows no starting material remaining. Concentration in vacuo is followed by neutralization of the mixture with 6N sodium hydroxide until the pH reaches 7—8. The amino acid thus obtained is purified by recrystallization or chromatography. This product is then methylated with diazomethane as described in Preparation 1 and 2. Purification affords the titled product.

Example 9

[5-(3-Pyridinylmethylamino)-2-methyl-phenoxy]-acetic Acid, Methyl Ester

Refer to Chart B (conversion of B—5 to B—6 wherein m is 1, $R_2$ is ortho —$CH_3$, $Y_1$ is —O—, n is 1)

A round-bottomed flask equipped with a magnetic stirring bar, a Dean-Stark moisture receiver, and a reflux condenser is charged with 1.95 g (10 mmol) of (4-amino-2-methyl-phenoxy)-acetic acid, methyl ester (Preparation 6) 1.07 g (10 mmol) of p-toluene sulfonic acid, and 60 ml of benzene-glyme (5:1). The resulting solution is heated at reflux temperature until TLC analysis shows no starting material remaining. The solvent is removed in vacuo and the residue is dissolved in 50 ml of methanol and is cooled to 0—5°C. Sodium borohydride powder (1.14 g, 30 mmol) is added over a period of 5 minutes. After stirring until TLC analysis shows no starting material remaining, the reaction is quenched with 25 ml of saturated aqueous ammonium chloride and the methanol is removed in vacuo. The residue is extracted with ethyl acetate and the organic layer is washed with 1N aqueous sodium hydroxide, brine, and dried over anhydrous magnesium sulfate. Filtration and concentration afford the crude product which is purified either by chromatography or recrystallization to give the titled product.

Example 10

[5-(3-Pyridinylmethlamino)-2-methyl-phenoxy]-acetic Acid, Sodium Salt (The sodium salt of Example 9)

A round-bottomed flask equipped with a magnetic stirring bar is charged with 1.4 g (5.0 mmol) of the compound of Example 9, 5.1 ml (5.1 mmol) of 1N aqueous sodium hydroxide, and 5.1 ml of methanol under a nitrogen atmosphere. The mixture is stirred at room temperature until TLC analysis shows no starting

material remaining. The mixture is lyophilized and recrystallized from acetone-water (or acetonitrile-water) to give the titled product.

Preparation 7

4-Acetamidothiphenoxy-acetic Acid, Methyl Ester

Refer to Chart B (conversion of B—3 to B—4 wherein $R_2$ is —H, $Y_1$ is —S), n is 1).

A round-bottomed flask equipped with a magnetic stirring bar is charged with 16.7 g (0.1 mol) of 4-acetamidothiophenol (Aldrich), 16.6 g (0.12 mol) of potassium carbonate, 30.6 g (0.2 mol) of bromoacetate (Aldrich), and 200 ml of glyme. The mixture is stirred at room temperature until TLC analysis shows no starting material. Work-up is undertaken as described in Preparation 5 to give the titled product.

Preparation 8

(4-Amino-thiophenoxy)-acetic Acid, Methyl Ester

Refer to Chart B (conversion of B—4 to B—5 wherein $R_2$ is —H, $Y_1$ is —S—, n is 1)

Following the procedure described in Preparation 6, 4-acetamido-thiophenoxy-acetic acid, methyl ester (Preparation 7) is converted to the titled product.

Example 11

[5-(3-Pyridinylmethylamino)thiophenoxy]-acetic Acid, Methyl Ester

Refer to Chart B (conversion of B—5 to B—6 wherein m is 1, $R_2$ is —H, $Y_1$ is —S—, n is 1).

Following the procedure described in Example 9, (4-aminothiophenoxy)-acetic acid, methyl ester (Preparation 8) is reacted with 3-pyridinecarboxaldehyde (B—5A wherein m is 1) to yield the titled product.

Example 12

[5-(3-Pyridinylmethylamino)-thiphenoxy]-acetic Acid, Sodium Salt

Refer to Chart B (conversion of B—6 to B—7 wherein m is 1, $R_2$ is —H, $Y_1$ is —S—, n is 1).

Following the procedure described in Example 10, [5-(3-pyridinylmethylamino)-thiophenoxy]-acetic acid methyl ester (Example 11) is converted to the titled product.

Preparation 9

5-(3-Pyridinylmethylamino)-2-hydroxy-nitrobenzene

Refer to Chart C (conversion of C—1 to C—2 wherein M is 1, $R_2$ is —OH).

Following the procedure described in Example 9, 4-amino-2-nitrophenol (Aldrich) is reacted with 3-pyridinecarboxaldehyde (C—1A wherein m is 1) to yield the titled product.

Preparation 10

5-(3-Pyridinylmethylamino-N-acetyl)-2-acetoxy-nitrobenzene

Refer to Chart C (conversion of C—2 to C—3 wherein M is 1, $R_2$ is —OAc).

Following the procedure described in Preparation 3, 5-(3-pyridinylmethylamino)-2-hydroxy-nitrobenzene (Preparation 9) is converted to the titled product.

Preparation 11

5-(3-Pyridinylmethylamino-N-acetyl)-2-acetoxy-aminobenzene

Refer to Chart C (conversion of C—3 to C—4 wherein m is 1, $R_2$ is —OAc).

Following procedures known in the art (e.g., $Et_3N.HCO_2H$, Pt/C or $H_2$/Ru catalyst), the nitro group in (3-pyridinylmethyl amino-N-acetyl)-2-acetoxy-nitrobenzene (Preparation 10) is reduced to an amino group to yield the titled product.

Preparation 12

5-(3-Pyridinylmethylamino-N-acetyl)-2-hydroxy-aminobenzene-N-acetic Acid, Methyl Ester

Refer to Chart C (conversion of C—4 to C—5 wherein m is 1, $R_2$ is —OH, n is 1).

Following the procedure described in Preparation 3, 5-(3-pyridinylmethylamino-N-acetyl)-2-acetoxy-aminobenzene (Preparation 11) is thermally condensed with the methyl ester of glyoxalic acid (C—4A wherein n is 1, $R_1$ is $—CH_3$) to yield the corresponding imine which is reduced with sodium borohydride to yield the titled product. The acetoxy group attached to the benzene ring is also hydrolyzed by sodium borohydride.

Example 13

5-(3-Pyridinylmethylamino)-2-hydroxy-aminobenzene-N-acetic Acid, Methyl Ester

Refer to Chart C (conversion of C—5 to C—6 wherein m is 1, $R_2$ is —OH, n is 1).

Following the procedure described in preparation 6, 5-(3-pyridinylmethyl(amino-N-acetyl)-2-hydroxy-aminobenzene-N-acetic acid, methyl ester (Preparation 12) is converted to the titled product.

Example 14

5-(3-Pyridinylmethylamino)-2-hydroxy-aminobenzene-N-acetic Acid, Sodium Salt

Refer to Chart C (conversion of C—6 to C—7 wherein m is 1, $R_2$ is —OH, n is 1).

Following the procedure described in Example 2, 5-(3-pyridinylmethylamino)-2-hydroxy-aminobenzene-N-acetic acid, methyl ester, is converted to the titled product.

Example 13

5-(3-Pyridinylmethylamino-N-acetyl)-2-acetoxy-N-acetyl-aminobenzene

Refer to Chart C (conversion of C—4 to C—8 wherein m is 1, $R_2$ is —OAc).

Following the procedure described in Preparation 3, 5-(3-pyridinylmethylamino-N-acetyl)-2-acetoxy-aminobenzene (Preparation 11) is converted to the titled product.

Preparation 14

5-(3-Pyridinylmethylamino-N-acetyl)-2-acetoxy-N-acetyl-aminobenzene-N-acetic Acid, Methyl Ester

Refer to Chart C (conversion of C—8 to C—9 wherein m is 1, $R_2$ is —OAc).

Utilizing sodium hydride as the base and DMF as the solvent, the anion of 5-(3-pyridinylmethylamino-N-acetyl)-2-acetoxy-N-acetyl-aminobenzene (Preparation 13) is alkylated with bromoacetate (Aldrich) to give the titled product.

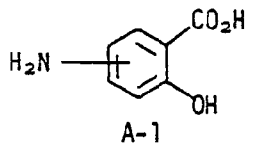
Example 15

5-(3-Pyridinylmethylamino)2-hydroxy-aminobenzene-N-acetic Acid, Methyl Ester

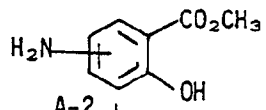
Refer to Chart C (conversion of C—9 to C—6 wherein m is 1, $R_2$ is —OH, n is 1).

Following the procedure described in Example 13, 5-(3-pyridinylmethylamino-N-acetyl)-2-acetoxy-N-acetyl-aminobenzene-N-acetic acid, methyl ester, (Preparation 14) is converted to the titled product.

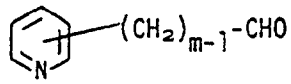
CHART A



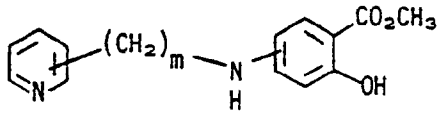
A-1



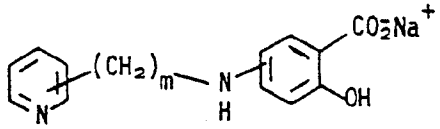
A-2



A-2A

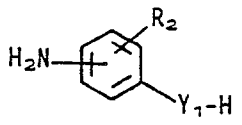


A-3

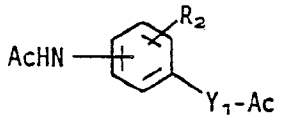


A-4

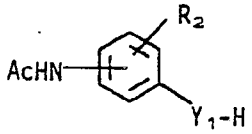
CHART B



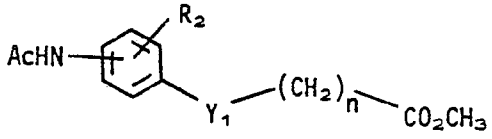

B-1




B-2

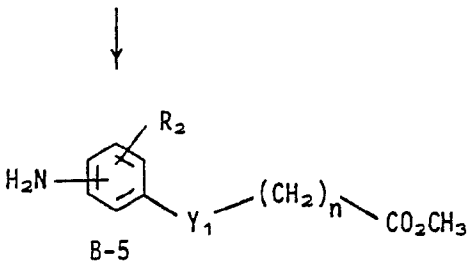



B-3

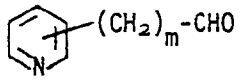



B-4

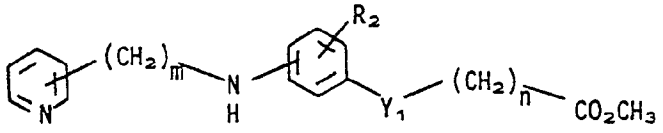
CHART B (continued)



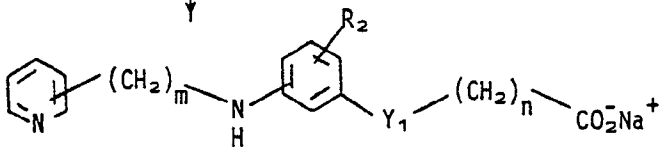
B-5



B-5A



B-6



B-7

CHART C

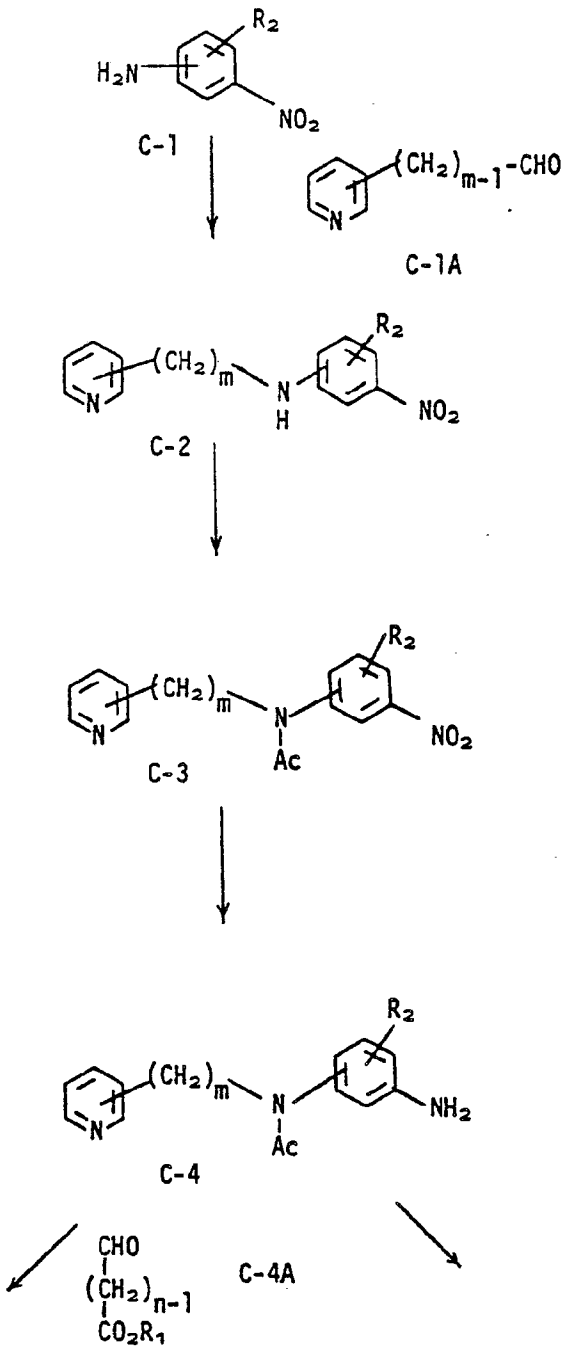
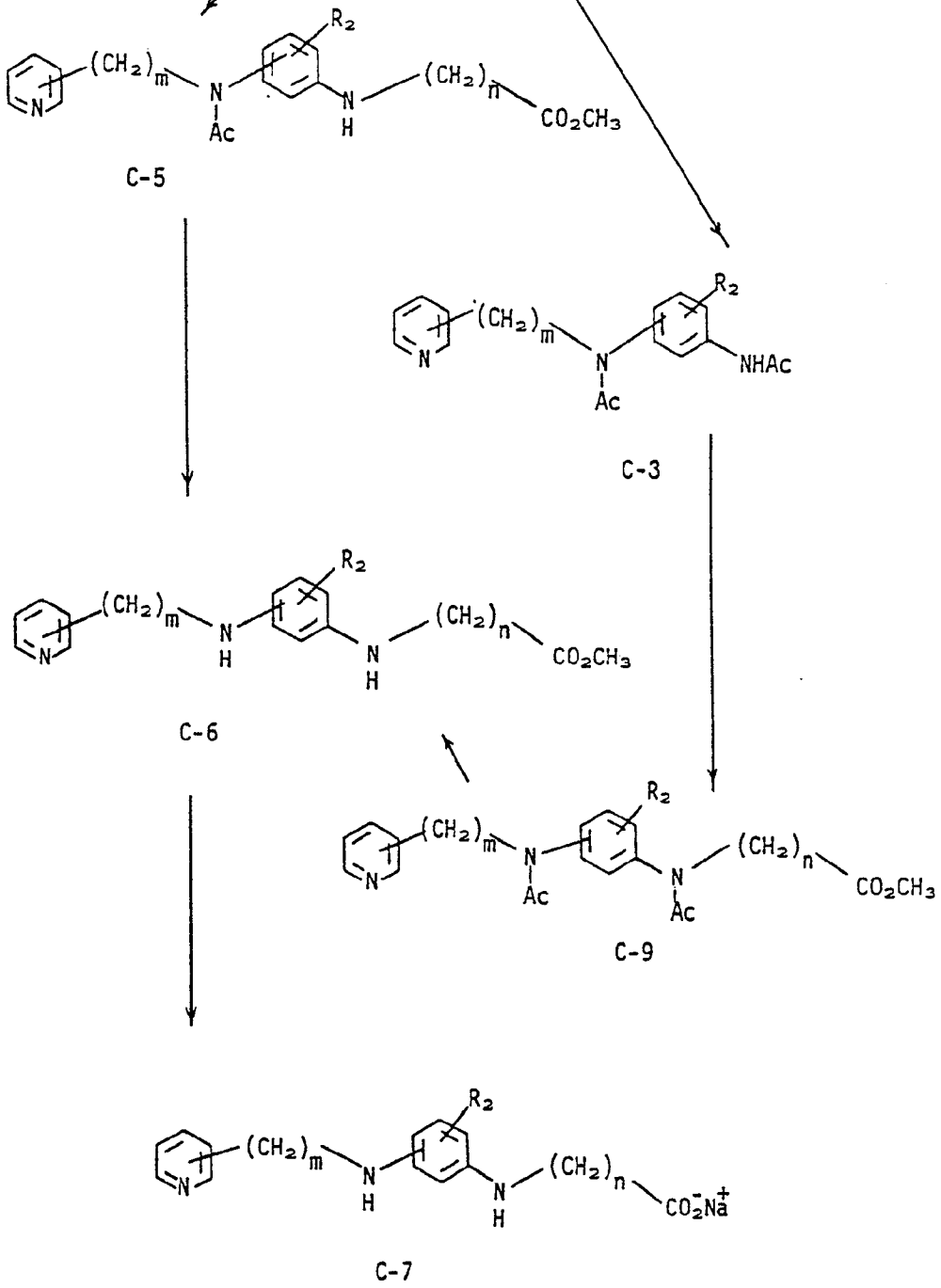
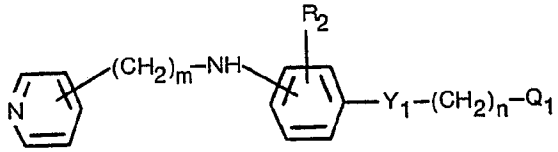

R2
H2N
NO2
C-1
(CH2)m-1-CHO
N
C-1A
(CH2)m
N
H
NO2
C-2
(CH2)m
N
Ac
NO2
C-3
(CH2)m
N
Ac
NH2
C-4
CHO
(CH2)n-1
CO2R1
C-4A

CHART C (continued)



**Claims**

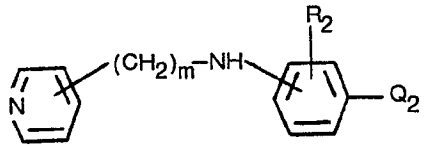
1. A compound of the formula



I

wherein m is an integer of from one to 6;
n is an integer of from one to 6;
$Y_1$ is —O—, —S—, —$NR_3$— or a valence bond;
$R_2$ is H, OH, $OCH_3$, $OOCCH_3$, F, Cl, Br, $CH_3$, $CF_3$, $N(CH_3)_2$, $NO_2$, SH or $SCH_3$; and
$Q_1$ is $COOR_1$, $CH_2OH$, $CH_2SH$, $NHR_3$ or 1-tetrazolyl;
in which $R_1$ is selected from hydrogen, a pharmacologically acceptable cation, $C_{1-12}$ alkyl, $C_{3-10}$ cycloalkyl, $C_{7-12}$ aralkyl, phenyl, phenyl substituted up to 3 times by chlorine atoms or $C_{1-3}$ alkyl groups, or phenyl para-substituted by acetamido, benzamido, acetamidobenzamido, benzamidobenzamido, ureido, acetoxy, benzyloxy, aminocarbonyloxy, methoxycarbonyloxy, benzoyl, acetamidobenzoyl, acetamidobenzoyloxy or ureidoiminomethyl; and $R_3$ is hydrogen, $C_{1-5}$ alkyl or CHO,
or a pharmacologically acceptable acid addition salt thereof.

2. A compound of the formula



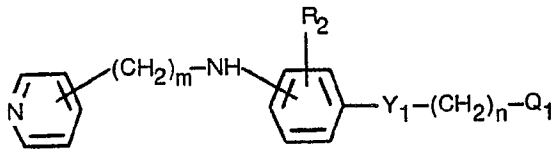
II

wherein $Q_2$ is $COOR_1$ or 1-tetrazolyl and m, $R_1$ and $R_2$ are as defined in claim 1,
or a pharmacologically acceptable acid addition salt thereof,
with the proviso that $R_2$ is OH when $Q_2$ is $COOR_1$ and $R_1$ is hydrogen, alkyl or a pharmacologically acceptable cation.

3. A compound of claim 1, wherein m is one, $Y_1$ is —O—, $Q_1$ is $COOR_1$ and $R_1$ is as defined in claim 1.
4. A compound of claim 2, wherein m is one.
5. A compound of claim 2 wherein $Q_2$ is $COOR_1$.
6. A compound of claim 3, 4 or 5, wherein $R_1$ is H, $CH_3$, Na, K or Ca, and $R_2$ is H, OH, $CH_3$, $OOCCH_3$, F or $CF_3$.
7. 4-(3-Pyridinylmethylamino)salicylic acid, methyl ester or sodium salt.
8. 5-(3-Pyridinylmethylamino)salicylic acid, methyl ester or sodium salt.
9. 5-(2-Pyridinylmethylamino)salicylic acid, methyl ester or sodium salt.
10. 5-(4-Pyridinylmethylamino)salicylic acid, methyl ester or sodium salt.
11. [5-(3-Pyridinylmethylamino)-2-methylphenoxy]acetic acid, methyl ester or sodium salt.
12. [5-(3-Pyridinylmethylamino)thiophenoxy]acetic acid, methyl ester or sodium salt.
13. 5-(3-Pyridinylmethylamino)-2-hydroxyaniline-N-acetic acid, methyl ester or sodium salt.

**Patentansprüche**

1. Eine Verbindung der Formel



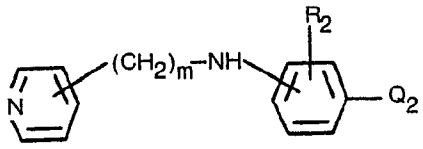
I

wobei m ein Integer von eins bis 6 ist;
n ist ein Integer von eins bis 6:
$Y_1$ ist —O—, —S—, —$NR_3$— oder eine Valenzbindung;
$R_2$ ist H, OH, $OCH_3$, $OOCCH_3$, F, Cl, Br, $CH_3$, $CF_3$, $N(CH_3)_2$, $NO_2$, SH oder $SCH_3$; und
$Q_1$ ist $COOR_1$, $CH_2OH$, $CH_2SH$, $NHR_3$ oder 1-Tetrazolyl;
wobei $R_1$ gewählt ist von Wasserstoff, einer pharmakologisch akzeptablen Kation, $C_{1-12}$Alkyl, $C_{3-10}$Cycloalkyl, $C_{7-12}$Aralkyl, Phenyl, Phenyl substituiert bis zu dreimal durch Chloratome oder

$C_{1-3}$Alkylgruppen, oder Phenyl para-substituiert duch Acetamido, Benzamido, Acetamidobenzamido, Benzamidobenzamido, Ureido, Acetoxy, Benzyloxy, Aminocarbonyloxy, Methoxycarbonyloxy, Benzoyl, Acetamidobenzoyl, Acetamidobenzoyloxy oder Ureidoiminomethyl; und $R_3$ ist Wasserstoff, $C_{1-5}$ Alkyl oder CHO

oder ein pharmakologisch akzeptables saures Zusatzsalz davon.

2. Eine Verbindung der Formel



II

wobei $Q_2$ $COOR_1$ oder 1-Tetrazolyl ist und m, $R_1$ und $R_2$ wie in Anspruch 1 definiert sind,

oder ein pharmakologisch akzeptables saures Zusatzsalz davon;

unter der Voraussetzung, daß $R_2$ OH ist, wenn $Q_2$ $COOR_1$ ist und $R_1$ ist Wasserstoff, Alkyl oder eine pharmakologisch akzeptable Kation.

3. Eine Verbindung von Anspruch 1, worin m eins ist, $Y_1$ ist —O—, $Q_1$ ist $COOR_1$ und $R_1$ ist definiert wie in Anspruch 1.

4. Eine Verbindung von Anspruch 2, worin m eins ist.

5. Eine Verbindung von Anspruch 2, worin $Q_2$ $COOR_1$ ist.

6. Eine Verbindung von Anspruch 3, 4 oder 5, worin $R_1$ H, $CH_3$, Na, K oder Ca ist, und $R_2$ ist H, OH, $CH_3$, $OOCCH_3$, F oder $CF_3$.

7. 4-(3-Pyridinylmethylamino)Salicylsäure, Methylester oder Natriumsalz.

8. 5-(3-Pyridinylmethylamino)Salicylsäure, Methylester oder Natriumsalz.

9. 5-(2-Pyridinylmethylamino)Salicylsäure, Methylester oder Natriumsalz.

10. 5-(4-Pyridinylmethylamino)Salicylsäure, Methylester oder Natriumsalz.

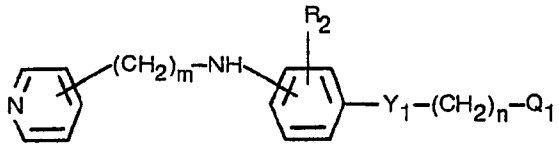
11. [5-(3-Pyridinylmethylamino)-2-Methylphenoxy) Essigsäure, Methylester oder Natriumsalz.

12. [5-(3-Pyridinylmethylamino)Thiophenoxy) Essigsäure, Methylester oder Natriumsalz.

13. 5-(3-Pyridinylmethylamino)-2-Hydroxyanilin-N-Essigsäure, Methylester oder Natriumsalz.

**Revendications**

1. Composé de formule



I

dans laquelle m est un nombre entier de 1 à 6;

n est un nombre entier de 1 à 6;

$Y_1$ représente —O—, —S—, —$NR_3$— ou une liaison de valence;

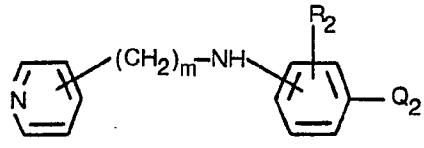
$R_2$ représente H, OH, $OCH_3$, $OOCCH_3$, F, Cl, Br, $CH_3$, $CF_3$, $N(CH_3)_2$, $NO_2$, SH ou $SCH_3$; et

$Q_1$ est un groupe $COOR_1$, $CH_2OH$, $CH_2SH$, $NHR_3$ ou 1-tétrazolyle;

où $R_1$ est choisi entre l'hydrogène, un cation acceptable du point de vue pharmacologique, un groupe alkyle en $C_1$ à $C_{12}$, cycloalkyle en $C_3$ à $C_{10}$, aralkyle en $C_7$ à $C_{12}$, phényle, phényle substitué jusqu'à 3 fois par des atomes de chlore ou des groupes alkyle en $C_1$ à $C_3$ ou phényle substitué en para par un groupe acétamido, benzamido, acétamidobenzamido, benzamidobenzamido, uréido, acétoxy, benzyloxy, aminocarbonyloxy, méthoxycarbonyloxy, benzoyle, acétamidobenzoyle, acétamidobenzoyloxy ou uréidoiminométhyle; et $R_3$ est l'hydrogène, un groupe alkyle en $C_1$ à $C_5$ ou CHO

ou un sel d'addition d'acide pharmacologiquement acceptable de ce composé.

2. Composé de formule



II

dans laquelle $Q_2$ est un groupe $COOR_1$ ou 1-tétrazolyle et m, $R_1$ et $R_2$ ont les définitions données dans la revendication 1,

ou un sel d'addition d'acide pharmacologiquement acceptable de ce composé

sous réserve que $R_2$ soit un groupe OH lorsque $Q_2$ est un groupe $COOR_1$ et $R_1$ est l'hydrogène, un groupe alkyle ou un cation pharmacologiquement acceptable.

3. Composé suivant la revendication 1, dans lequel m est égal à 1, $Y_1$ représente —O—, $Q_1$ est un groupe $COOR_1$ et $R_1$ est tel que défini dans la revendication 1.

4. Composé suivant la revendication 2, dans lequel m est égal à un.

5. Composé suivant la revendication 2, dans lequel $Q_2$ est un groupe $COOR_1$.

6. Composé suivant la revendication 3, 4 ou 5, dans lequel $R_1$ représente H, $CH_3$, Na, K ou Ca et $R_2$ représente H, OH, $CH_3$, $OOCCH_3$, F ou $CF_3$.

7. L'ester méthylique ou le sel de sodium de l'acide 4-(3-pyridinylméthylamino)salicylique.

8. L'ester méthylique ou le sel de sodium de l'acide 5-(3-pyridinylméthylamino)salicylique.

9. L'ester méthylique ou le sel de sodium de l'acide 5-(2-pyridinylméthylamino)salicylique.

10. L'ester méthylique ou le sel de sodium de l'acide 5-(4-pyridinylméthylamino)salicylique.

11. L'ester méthylique ou le sel de sodium de l'acide [5-(3-pyridinylméthylamino)-2-méthylphénoxy]-acétique.

12. L'ester méthylique ou le sel de sodium de l'acide [5-(3-pyridinylméthylamino)thiophénoxy) acétique.

13. L'ester méthylique ou le sel de sodium de l'acide 5-(3-pyridinylméthylamino)-2-hydroxyaniline-N-acétique.